51. (New) The method of claim 33 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

52. (New) The method of claim 51 wherein the codon encoding amino acid 670 is mutated to encode Asn, and the codon encoding amino acid 671 is mutated to encode Leu.

53. (New) The method of claim 33 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{N3}(pE)$, $A\beta_{X-42}$, and $A\beta_{Insoluble}$.

54. (New) The method of claim 33 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding a human amyloid precursor protein.

55. (New) The method of claim 54 wherein the intron is an APP gene intron.

56. (New) The method of claim 33 wherein the region encoding a human amyloid precursor protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

Remarks

Claims 1-20, 22-26, and 28-56 are pending. Claims 1, 7, 9, 11, 13, 15, 17, 19, and 26 have been amended. Claims 21 and 27 have been canceled. Claims 28-56 have been

added. Claims 1, 7, 9, 11, 13, 15, 17, 19, and 26 have been amended to limit the transgenic mammal to mice. Support for this amendment, which merely narrows the scope of the claims, appears throughout the specification. Claim 1 has been amended to more clearly recite what applicants consider to be their invention. Specifically, claim 1 has been amended to require that the transgenic mammal develops plaques that stain with Congo red. Support for this amendment appears at least in original claim 27.

New claims 28 and 56 exclude the use of constructs that are a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8. Support for this amendment appears at least in the material added on page 28, and on page 66, lines 6-8, of the specification. New claims 29-32 correspond to, and find support in, claims 7, 8, 14, and 15, respectively, in parent Application Serial No. 08/659,797. New claims 33-45 and 47-52 correspond to, and find support in, claims 1-15, and 17-20, respectively, in parent Application Serial No. 08/480,653. New claims 46 and 53-55 correspond to, and find support in, claims 3, 2, 9, and 10, respectively, in parent Application Serial No. 08/486,538.

The material added to page 28 of the specification is supported at least by original claim 1 in each of Application Serial Nos. 08/660,487, 08/480,653, 08/486,538, and 08/659,797, and in Example 5, especially page 66, lines 6-8.

Favorable consideration of claims 1-20, 22-26, and 28-56 is respectfully requested.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.10

I hereby certify that this Preliminary Amendment and any documents referred to as attached therein are being deposited with the United States Postal Service on this date, September 8, 1998, in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R § 1.10, Mailing Label Number EM 500 209 605 US addressed to Box Patent Application, Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Robert A. Hodges

Date: September 8, 1998

1. A method for testing compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an Aβ-containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the Aβ-containing protein, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770, APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP695, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717,

wherein the Aβ-containing protein includes amino acids 672 to 714 of human APP,

wherein the region encoding an Aβ-containing protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8,

wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of brain tissue of the mouse when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of brain tissue of the mouse when it is two to four months old, APP and APPα combined are expressed at a level of at least 150 picomoles per gram of brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of brain tissue of the mouse when it is two to four months old, and/or mRNA encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in brain tissue of the mouse when it is two to four months old;

wherein the transgenic mouse develops plaques that stain with Congo red; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

2. The method of claim 1 wherein the Aβ-containing protein is selected from the group consisting of APP770; APP770 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP751; APP751 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP695; APP695 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; a protein consisting of amino acids 646 to 770 of APP; a protein consisting of amino acids 670 to 770 of APP; a protein consisting of amino acids 672 to 770 of APP; and a protein consisting of amino acids 672 to 714 of APP.

3. The method of claim 2 wherein the DNA encoding the Aβ-containing protein is cDNA or a cDNA/genomic DNA hybrid, wherein the cDNA/genomic DNA hybrid includes at least one APP intron sequence wherein the intron sequence is sufficient for splicing.

4. The method of claim 1 wherein the promoter is the human platelet derived growth factor β chain gene promoter.

5. The method of claim 1 wherein the region further comprises DNA encoding a second protein, wherein the DNA encoding the Aβ-containing protein and the DNA encoding the second protein are operative linked such that the region encodes an Aβ-containing fusion protein comprising a fusion of the Aβ-containing protein and the second protein.

6. The method of claim 5 wherein the second protein is a signal peptide.

7. The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

8. The method of claim 7 wherein the protein is selected from the group consisting of Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1α, IL-1β, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1,

lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100β, $cPLA_2$, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-B, IκB, NFκB, IL-8, MCP-1, MIP-1α, matrix metaloproteinases, 4-hydroxynonenal-protein conjugates, amyloid P component, laminin, and collagen type IV.

9. The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

10. The method of claim 9 wherein the protein is selected from the group consisting of Cat D,B, protein kinase C, NADPH, C3d, C1q, C5, C4bp, C5a-C9, tau, ubiquitin, MAP-2, neurofilaments, heparin sulfate, chrondroitin sulphate, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glycosylation end products, amyloid P component, laminin, and collagen type IV.

11. The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

12. The method of claim 11 wherein the protein is selected from the group consisting of nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, glutamine synthetase, glucose transporter, PPI kinase, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, ubiquitin, and apolipoprotein E.

13. The method of claim 1 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

14. The method of claim 13 wherein the encoded protein is selected from the group consisting of growth inhibitory factor, Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine

synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1, lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100β, $cPLA_2$, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-B, IκB, NFκB, IL-8, MCP-1, MIP-1α, matrix metaloproteinases, 4-hydroxynonenal-protein conjugates, amyloid P component, laminin, and collagen type IV.

15. The method of claim 1 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

16. The method of claim 15 wherein the behavior is selected from the group consisting of behavior using working memory, behavior using reference memory, locomotor activity, emotional reactivity to a novel environment or to novel objects, and object recognition.

17. The method of claim 1 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or severity of the histopathology present in the transgenic mouse to which the compound has been administered.

18. The method of claim 17 wherein the histopathology marker is selected from the group consisting of compacted plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density, and neuropil abnormalities.

19. The method of claim 1 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

20. The method of claim 1 wherein the marker is detected or measured using RT-PCR, RNase protection, Northern analysis, R-dot analysis, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

22. The method of claim 1 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

23. The method of claim 22 wherein the codon encoding amino acid 717 is mutated to encode Phe.

24. The method of claim 1 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and/or

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Leu, Tyr, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

25. The method of claim 24 wherein the codon encoding amino acid 670 is mutated to encode Asn, and/or the codon encoding amino acid 671 is mutated to encode Leu or Tyr.

26. The method of claim 1 wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APP and APPα combined are expressed at a level of at least 150 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, and/or mRNA encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in hippocampal or cortical brain tissue of the mouse when it is two to four months old.

28. The method of claim 1 wherein the region encoding an Aβ-containing protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

29. The method of claim 7 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{N3}$(pE), $A\beta_{X-42}$, $A\beta_{X-40}$, $A\beta_{Insoluble}$, $A\beta_{Soluble}$, full length APP, APPα, APPβ, FLAPP+ APPα, the last 100 amino acids of APP, and the last 57 to 60 amino acids of APP.

30. The method of claim 17 wherein the Alzheimer's disease marker is selected from the group consisting of APP695, APP751, and APP770, and wherein the change in

histopathology is a reduction in the amount of Alzheimer's disease marker localized in plaques and neuritic tissue.

31. The method of claim 1 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding the Aβ-containing protein.

32. The method of claim 30 wherein the intron is an APP gene intron.

33. A method for screening compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell operatively linked to a region of the construct encoding a human amyloid precursor protein,

wherein the region of the construct encoding a human amyloid precursor protein is selected from the group consisting of APP770 cDNA; APP770 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP751 cDNA; APP751 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695 cDNA; the APP695 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695, APP751, or APP770 cDNA truncated at amino acid 671 or 685; APP cDNA truncated to encode amino acids 646 to 770 of APP; a combination cDNA/genomic APP gene construct; a combination cDNA/genomic APP gene construct bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; and a combination cDNA/genomic APP gene construct truncated at amino acid 671 or 685;

wherein Aβ is expressed at a level of at least 50 ng/g brain tissue in the transgenic mouse when the transgenic mouse is three months of age;

wherein the transgenic mouse develops plaques that stain with Congo red; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

34. The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

35. The method of claim 34 wherein the protein is selected from the group consisting of Cat D,B, Neuronal Thread Protein (CSF), nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

36. The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

37. The method of claim 36 wherein the protein is selected from the group consisting of Cat D,B, protein kinase C, NADPH, C3d, C1q, C5, C4bp, C5a-C9, tau, ubiquitin, MAP-2, neurofilaments, heparin sulfate, chrondroitin sulphate, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

38. The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

39. The method of claim 38 wherein the protein is selected from the group consisting of nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, glutamine synthetase, glucose transporter, PPI kinase, cytochrome oxidase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, ubiquitin, and apolipoprotein E.

40. The method of claim 33 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been

administered, or in cells derived from the transgenic mouse to which the compound has been administered.

41. The method of claim 40 wherein the protein is selected from the group consisting of growth inhibitory factor, Cat D,B, Neuronal Thread Protein (CSF), nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

42. The method of claim 33 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

43. The method of claim 42 wherein the behavior is selected from the group consisting of behavior using working memory, behavior using reference memory, locomotor activity, emotional reactivity to a novel environment or to novel objects, and object recognition.

44. The method of claim 33 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or severity of the histopathology present in the transgenic mouse to which the compound has been administered.

45. The method of claim 44 wherein the histopathology is selected from the group consisting of compacted plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density, and neuropil abnormalities.

46. The method of claim 44 wherein the Alzheimer's disease marker is selected from the group consisting of APP695, APP751, and APP770, and wherein the change in histopathology is a reduction in the amount of the marker localized in plaques and neuritic tissue.

47. The method of claim 33 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

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48. The method of claim 33 wherein the marker is detected or measured using RT-PCR, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

49. The method of claim 33 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

50. The method of claim 49 wherein the codon encoding amino acid 717 is mutated to encode Phe.

51. The method of claim 33 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

52. The method of claim 51 wherein the codon encoding amino acid 670 is mutated to encode Asn, and the codon encoding amino acid 671 is mutated to encode Leu.

53. The method of claim 33 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{N3}(pE)$, $A\beta_{X-42}$, and $A\beta_{Insoluble}$.

54. The method of claim 33 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding a human amyloid precursor protein.

55. The method of claim 54 wherein the intron is an APP gene intron.

56. The method of claim 33 wherein the region encoding a human amyloid precursor protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

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